

How atopic is atopic dermatitis?

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Background: The extent to which the phenotype of atopic dermatitis (AD) is truly atopic has been the subject of much debate.

Objective: We sought to systematically evaluate the evidence for the value of measurement of IgE antibodies in diagnosing AD and whether knowledge of IgE sensitization increases clinical diagnostic and predictive ability.

Methods: We searched Medline from its inception until September 2003. Only studies that measured atopy as either skin prick test positivity or IgE-antibody sensitization to environmental allergens were included within a descriptive analysis. Because the small number of studies of adequate quality did not allow a formal meta-analysis, we assigned strength of evidence according to predefined quality criteria and ranked studies accordingly.

Results: Inclusion of atopy as part of the diagnostic criteria for AD did not enhance the criteria's sensitivity and specificity in relation to the clinical phenotype of AD. The strength of association between atopy and AD varied significantly between hospital studies (47% to 75%; n = 14 studies) and was stronger in hospital than in community populations (7.4% to 78%; n = 13 studies). Whereas study quality did not have an effect on atopy prevalence in hospital populations, low atopy prevalences in community surveys were seen in less rigidly conducted studies. AD severity was positively associated with the number of positive skin prick test responses or IgE-antibody levels in 7 of 8 studies that measured both. Only one study suggested that IgE-specific sensitization to hen's egg is associated with subsequent development of AD, and 2 studies found that allergen-specific IgE sensitization in patients with AD is a prognostic marker for allergic airway disease in later life. Atopy-associated AD might also have a worse long-term prognosis than AD that is not associated with atopy.

Conclusion: Although atopy is clearly associated with AD, the role of IgE sensitization in AD needs further study. Current evidence suggests that up to two thirds of persons with AD are not atopic, which implies that continued use of the term *atopic dermatitis* is problematic. Longitudinal studies are needed to compare the treatment response and prognosis of IgE-associated and non-IgE-associated AD. (J Allergy Clin Immunol 2004;114:150-8.)

Key words: Atopic dermatitis, eczema, atopy, epidemiology

Abbreviations used

AD: Atopic dermatitis
EAACI: European Academy of Allergy and Clinical Immunology
SPT: Skin prick test
WAO: World Allergy Organization

It has been 35 years since the discovery of IgE.¹ From early on, it became apparent that many individuals with clinical allergic disease had very high serum total IgE levels. This was particularly the case for patients with atopic dermatitis (AD). However, the link between AD and allergen-specific IgE sensitization remains uncertain and hotly debated. This debate has been complicated by changing definitions of what constitutes an atopic individual.² In the past, the European Academy of Allergy and Clinical Immunology (EAACI) Nomenclature Task Force has defined the term *atopy* as a personal tendency, familial tendency, or both, usually in childhood and adolescence, to become sensitized and produce IgE antibodies.³ The EAACI also introduced the transitional term *atopic eczema—dermatitis syndrome* to denote AD. Most recently, the entire nomenclature of allergic skin diseases has been further updated by the World Allergy Organization (WAO) Nomenclature Review Committee.⁴

Up to 80% of AD cases are said to be associated with atopy,⁵ and proponents of different diagnostic criteria for AD have argued for and against the inclusion of increased total IgE levels or the presence of IgE sensitization as an essential diagnostic criterion in AD.^{6,7} This debate has almost exclusively been informed by hospital studies. Because hospital cases of AD tend to be more severe than cases in community settings,⁸ this might have led to an overemphasis of a phenomenon that might be at least partly related to disease severity.⁹

Beyond the role of IgE as part of the diagnostic criteria, it is frequently unclear whether IgE sensitization has a place in AD management and research or whether AD in an atopic child can reliably predict allergic asthma or rhinitis. This, coupled with the recent change in nomenclature, provides a good opportunity to critically appraise the value of IgE measurements in patients with AD. In particular, we asked the following questions: (1) How atopic is AD at a population level? (2) How useful is the knowledge of IgE sensitization in discriminating between the phenotype of AD and other skin diseases or persons without skin disease? (3) Is IgE sensitization in patients with AD a predictor of allergic airway disease in later life? (4) Does knowledge of IgE sensitization

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increase our clinical predictive abilities in terms of overall disease prognosis or responsiveness to treatment?

METHODS

We conducted a systematic review of the literature through searches of Medline from inception to the end of September 2003. Clear and explicit criteria for electronic searches were derived. The search terms included the Cochrane Skin Group search strategy for AD and "Immunoglobulin E" plus a search filter for population-based studies, "prevalence," and "epidemiology," as well as search filters for "diagnosis" and "prognosis" (Table I). The online search was supplemented by an extensive hand search of the literature. No restrictions were imposed with regard to language of publication. We also contacted experts in the field where this seemed appropriate. Each relevant article underwent standard pro forma data extraction by the first author, and all data were then assessed by the author panel.

Our literature search identified a total of 127 articles related to AD and IgE. We included studies in the analysis only if they defined atopy as either skin prick test (SPT) positivity or serum IgE antibodies to common environmental allergens, as proposed in the new EAACI/WAO nomenclature.^{3,4} No other exclusion criteria were used. This reduced the total number of original articles included in this systematic review from 127 to 65.

We collected articles to answer 4 separate questions on the relationship between atopy and AD. The number of studies related to each of the 4 questions was too small to allow formal meta-analysis. Formal meta-analysis was also not considered appropriate because of heterogeneity in study design, types of participants, and diagnostic criteria. We therefore assigned an empirically derived strength-of-evidence score to all articles that described the following main criteria: diagnostic criteria (clear validated criteria or physician diagnosis, 1; no clear diagnostic criteria, 0), study size (n of ≥ 500 , 1; n of < 500 , 0), and atopy measurement (≥ 5 allergens tested, 1; < 5 allergens tested, 0). For studies on disease severity, a score for methods of severity measurement was added (validated severity measurement, 1; severity measurement not validated, 0). Studies were then ranked by overall score and abstracted into tables. Studies of the same quality score were ranked by number of participants.

RESULTS

How atopic is AD at the population level?

Comparison between hospital and community populations. Out of 65 studies, we found 12 cross-sectional hospital surveys that examined the association between atopy and AD and that described study size, diagnostic methods, and atopy measurement tools. Atopy prevalences ranged from 47% to 75% (Table II).¹⁰⁻²¹ Lower levels of atopy-AD association were seen in cross-sectional population-based studies. Thirteen of 65 surveys were identified, and atopy prevalences ranged from 7% to 78% (Table III).²²⁻³¹ The overall atopy prevalence in the hospital populations was not related to study quality. In fact, the lowest prevalence (47%) was seen in the highest-scoring study. This was different in population-based samples, in which large studies that applied rigid diagnostic criteria found a stronger association between atopy and AD. Three of the 12 cross-sectional hospital studies performed either IgE antibody measurements or SPTs to foods alone, and a large number of participants were infants, whereas participants in the population-based surveys were 4 years of age or older, and all were tested for aeroallergens. Four

TABLE I. Medline search strategy

1. explode DERMATITIS, ATOPIC/
2. atopic dermatitis.mp.
3. dermatitis atopic.mp.
4. explode ECZEMA/
5. childhood eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
6. infantile eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
7. or/1-6
8. immunoglobulin E.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
9. explode Immunoglobulin E/
10. 8 or 9
11. 7 and 10
12. explode "Sensitivity and Specificity"/
13. explode Diagnostic Errors/
14. explode Mass Screening/
15. 12 or 13 or 14
16. 11 and 15
17. explode INCIDENCE/
18. explode MORTALITY/
19. mo.fs.
20. explode PROGNOSIS/
21. prognos\$.tw.
22. or/17-21
23. explode Cohort Studies/
24. cohort.tw.
25. explode Survival Analysis/
26. 23 or 24 or 25
27. 11 and 22 and 26
28. review literature.pt.
29. review academic.pt.
30. review tutorial.pt.
31. (systematic\$ and (review\$ or overview\$)).mp.
32. (meta?anal\$ or meta analy\$).mp.
33. or/28-32
34. 11 and 33
35. cross-section\$ stud\$.tw.
36. cross-section\$ research.tw.
37. (population\$ adj stud\$).tw.
38. longitudinal stud\$.tw.
39. longitudinal research.tw.
40. (cohort adj stud\$).tw.
41. case control.tw.
42. (follow up adj stud\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
43. (prospective adj stud\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject, heading]
44. or 35-44
45. 11 and 44

\$. Truncation symbol; *tw*, text words; *adj*, adjacent; *mp*, title, abstract, chemical abstracts (cas) registry/enzyme commission number (ec number) word, MESH subject heading.

of 13 community studies also performed testing for sensitization to foods.

Does the degree of association between atopy and AD depend on geography?

We also explored whether the association between atopy and AD depended on where the study was

TABLE II. Atopy and AD in hospital-based studies

Reference	Study size	Age	Diagnostic criteria*	% atopy (95% CI); tests performed†	Quality score (1-3)
Bergmann et al, ¹¹ 1998 (Germany)	1004	5 y	Clear	47% (44% to 50%); RAST f + ae	3
Guillet et al, ¹² 1992 (France)	250	<2-16 y	Clear	67% (61% to 73%); SPT f + ae	2
Murphy et al, ¹³ 1999 (United Kingdom)	142	1-18 y	Clear	75% (67% to 82%); RAST f + ae	2
Patrizi et al, ¹⁴ 2000 (Italy)	78	2 mo-3 y	Clear	47% (36% to 59%); SPT f + ae	2
Novembre et al, ¹⁰ 2001 (Italy)	77	2	Clear	64% (52% to 74%); SPT f + ae	2
Fabrizi et al, ¹⁵ 1999 (Italy)	72	1-25	Clear	44.4% (33% to 57%); RAST f + ae	2
Hochreutener, ¹⁶ 1991 (Switzerland)	40	5 mo-6 y	Clear	70% (53% to 83%); RAST and SPT f + ae	2
Wüthrich et al, ¹⁷ 2002 (Switzerland)	22	2-4	Clear	54% (32% to 77%); SPT f + ae	2
ETAC Study Group, ¹⁸ 1997 (Europe)	817	1-2	Not clear	60% (57% to 64%); RAST f + ae	2
Burks et al, ¹⁹ 1998 (United States)	165	4 mo-21 y	Clear	60% (52% to 68%); SPT f	1
Niggemann et al, ²⁰ 1999 (Germany)	107	5 mo-12 y	Clear	59% (49% to 68%); RAST f	1
Eigenmann et al, ²¹ 1998 (United States)	63	3 mo-19 y	Clear	65% (52% to 77%); RAST f	1

*Diagnostic criteria: *not clear*, not clearly defined or validated; *clear*, clearly defined and validated (ie, derivatives of Hanifin and Rajka's criteria or physician diagnosis).

†f, Food allergens; ae, aeroallergen.

conducted. Twelve of 65 community surveys calculated odds ratios to express the risk of being atopic as a patient with AD in comparison with the risk of being atopic as a healthy control subject. Whereas participants with AD in the United Kingdom, Germany, and Denmark were at a significantly increased risk of being atopic in comparison with healthy control subjects (odds ratio, 2.0-5.3), no statistically significant association was found in Hong Kong, China, Malaysia, Ethiopia, Costa Rica, and Sweden (Table III). However, all but one study without a significant association between atopy and AD used a questionnaire approach to identify participants with AD, and these studies were generally of lower quality than surveys that found statistically significant associations.

Is IgE sensitization a marker of severity in AD?

One explanation for the variation in the degree of association between atopy and AD in hospital and community studies is that these studies involved patients with differing disease severities, with the most severe cases being seen in hospital settings.⁸ Eight of 65 studies were identified that investigated the link between AD severity and atopy. Of these, 7 studies concluded that the number of SPTs, IgE-antibody specificities, and/or IgE

levels were significantly associated with AD severity (Table IV).^{12-14,16,22,32-34}

How useful is the knowledge of IgE sensitization in discriminating between the phenotype of AD and other skin diseases or persons without skin disease?

In 1977, Hanifin and Lobitz³⁵ suggested that measurements of IgE should be part of the diagnostic criteria for AD. These were formalized into major and minor criteria in 1980. One of the major criteria was a personal or family history of clinical allergic disease. In addition, increased total serum IgE level was included as a minor feature.³⁶ At the time, this was based on a consensus between experienced dermatologists rather than objective clinical validation. The so far only systematic evaluation of Hanifin and Rajka's diagnostic criteria, including specific IgE sensitization, has been performed in several studies by Diepgen et al (Table V).³⁷⁻³⁹ Although detectable IgE antibodies were significantly associated with AD, exclusion of specific IgE measurements from the diagnostic criteria did not change the criteria's sensitivity and specificity in logistic regression.³⁹ In other words, although there was statistical evidence of an association between AD and specific IgE, the latter was not a useful discriminator for AD once others factors had been taken into account.

TABLE III. Atopy and AD in population-based studies

Reference	Study population	Study size	Age (y)	Diagnostic criteria	No AD	AD	Odds ratio (95% CI)	Quality score (1-3)
					% atopic	% atopic		
Schäfer et al, ²² 1999 (Germany)	Schoolchildren	1845	5-14	Physician	36% RAST (ae)	75%	5.27 (2.54-11.15)	3
Schäfer et al, ²³ 2000 (Germany)	West German schoolchildren/East German schoolchildren	2075/ 1926	5-6/ 5-6	Physician/ physician	26%/23% SPT (ae + f)	50%/37%	2.84 (1.97-4.10)/1.97 (1.43-2.71)	3/3
Mortz et al, ²⁴ 2003 (Denmark)	Schoolchildren	1501	12-16	Physician	19% RAST (ae + f)/20% SPT (ae + f)	30%/64%	2.23 (1.65-3.25), 1.25 (0.77-2.02)†/ 6.78 (3.54-12.98), 2.50 (1.09-5.74)†	3
Arshad et al, ²⁵ 2001 (United Kingdom)	Unselected birth cohort	981	4	Physician	16% SPT (ae + f)	43%	3.86 (2.59-5.75)	3
Perkin et al, ²⁶ 2003 (United Kingdom)	Unselected birth cohort	614	5	Physician	12% SPT (ae + f)	33%	3.00 (1.78-4.92)	3
Hattevig et al, ²⁷ 1987 (Sweden)	Schoolchildren	242	10-14	Physician	18% RAST (ae)	27%	1.66 (0.72-3.85)	2
Soto-Quiros et al, ²⁸ 2002 (Costa Rica)	Schoolchildren	170	10-13	Questionnaire (validated)	76% SPT (ae)	78%	1.10 (0.50-2.40)	2
Yemaneberhan et al, ²⁹ 2003 (Ethiopia)	Cross-sectional household survey	12,876	5-60+	Questionnaire (unvalidated)	8% SPT (ae)	15%	1.99 (0.93-4.26)	2
Leung et al, ³⁰ 1994 (Southeast Asia)	Schoolchildren in Hong Kong/China (San Bu)/Malaysia (Kota Kinabalu)	1062/ 737/ 409	13.9/ 16.4/ 15.5 (mean)	Questionnaire (unvalidated)	21%/9%/4% SPT (ae)	23%/11%/7%	1.10 (0.70-1.80)*/ 1.10 (0.60-1.80)*/ 1.90 (0.60-5.60)*	2
Hesselmar et al, ³¹ 2001 (Sweden)	Schoolchildren	412	12	Questionnaire (unvalidated)	Not given SPT (ae)	Not given	1.40 (0.84-2.36)	1

f, Food allergens; ae, aeroallergen.

*Age- and sex-adjusted odds ratio.

†Excluding IgE-associated sensitization to inhalant aeroallergens as part of diagnostic criteria.

How useful is early atopy in predicting subsequent AD?

Only 3 studies of selected birth cohorts investigated whether IgE antibodies or SPT positivity in early life could predict later development of AD. Zeiger et al⁴⁰ found that SPT positivity to hen's egg at age 12 months had a positive predictive value of 32% for AD at age 7 years. These findings were echoed by Bergmann et al,⁴¹ who found no association between IgE antibody levels at 12 months and AD at 2 years. Conversely, Burr et al⁴² found a significant association between IgE antibody levels to hen's egg at 1 year of age and AD at 7 years (Table VI).⁴⁰⁻⁴² However, the latter study lacked clear diagnostic criteria for AD.

Is IgE sensitization in AD a predictor of allergic airway disease in later life?

Several descriptive studies suggested an association between AD and later allergic airway disease, especially if AD started in infancy and was severe.⁴³⁻⁴⁵ However, these studies did not differentiate between atopic and nonatopic children but suggested that the association between AD and later allergic respiratory disease

appeared particularly strong in those with a positive family history of allergic disease.⁴⁶ In addition, Novembre et al¹⁰ and Wüthrich et al¹⁷ recently showed, in 2 small longitudinal hospital studies (n = 77 and n = 22), that the risk of development of allergic respiratory disease appeared increased in patients with IgE-associated versus non-IgE-associated AD. The analysis in both studies was not adjusted for a family history of allergic disease.

Only very few surveys have systematically investigated the clinical predictive value of AD with and without coexisting atopy. Nickel et al⁴⁷ examined whether AD by age 12 months alone was an independent predictor of aeroallergen sensitivity at age 3 years but found no significant association (Table VII).⁴⁷⁻⁵³ These results have been echoed by Rhodes et al,⁵³ who found no link between AD before age 2 years and asthma by age 11 years. Kulig et al⁵² analyzed data from the German Multi Centre Allergy Study and found that all participants with AD and IgE sensitization to at least one food allergen at the age of 12 months had allergic airway disease by 5 years of age. However, patient numbers were very small (n = 6). Tariq et al⁴⁹ demonstrated a positive predictive value of 80% for AD plus SPT positivity to hen's egg at age 12 months for

TABLE IV. Atopy as a marker of AD severity

Reference	Study population	Design	Severity measure	IgE measure	Diagnostic criteria*	Quality score (1-4) and results
Schäfer et al, ²² 1999 (Germany)	2201 children, aged 5-14 y	Cross-sectional	SCORAD	Total IgE, RAST	Clear	4: Specific IgE score directly associated with AD severity.
Wolkerstorfer et al, ³² 2002 (Europe, ETAC)	397 children with AD and family history of allergic disease, aged 1-2 y	Longitudinal 18-mo follow-up	SCORAD	RAST	Clear	3: AD severity associated with sensitization to hen's egg and cow's milk. Specific IgE class significantly associated with SCORAD.
Böhme et al, ³³ 2001 (Sweden)	221 children with AD from community birth cohort	Longitudinal follow-up at 3, 6, and 12 mo	SCORAD	SPT, RAST	Clear	3: No association between SPT-RAST and SCORAD. Possibly caused by lack of patients with severe AD (only 2% of patients had severe AD).
Guillet et al, ¹² 1992 (France)	250 dermatology outpatients with mild-to-severe AD aged 2-16 y	Cross-sectional	Own severity score: mild, moderate, and severe	SPT	Clear	2: Number of positive SPT responses associated with AD severity. All patients with mild disease had negative responses, 33% of patients with moderate disease had at least 1 positive response, and all patients with severe disease had at least 1 positive SPT response.
Murphy et al, ¹³ 1999 (United Kingdom)	166 children with AD identified through a pediatric dermatology clinic	Cross-sectional	Rajka and Langeland	Total IgE, RAST	Clear	2: Both total serum IgE and specific IgE scores were significantly associated with AD severity.
Patrizi et al, ¹⁴ 2000 (Italy)	78 children with AD aged 2 mo-3 y	Longitudinal 4-y follow-up	Rajka and Langeland	Total IgE, SPT	Clear	2: Positive association between total IgE, SPT positivity, and AD.
Hochreutener et al, ¹⁶ 1991 (Switzerland)	40 pediatric dermatology outpatients with AD aged 5 mo-6 y	Cross-sectional	Own score	Total IgE, RAST, SPT	Clear	2: Positive association between AD severity, total IgE level, and aeroallergen but not food hypersensitivity.
Hill et al, ³⁴ 2000 (Australia)	A: 559 children from a birth cohort with a family history of allergic disease in a first-degree relative (→2 groups, one without AD and one with mild AD). B: 69 children with severe AD from an allergy center	Longitudinal 12-mo follow-up	Own score	Total IgE, SPT	Not clear	1: AD severity associated with specific IgE levels.

*Diagnostic criteria: *not clear*, not clearly defined or validated; *clear*, clearly defined and validated (ie, derivatives of Hanifin and Rajka's criteria or physician diagnosis).

TABLE V. IgE in the diagnosis of AD

Reference	Study population and sample size	Measurements	Outcome-results
Diepgen et al, ³⁷ 1990 (Germany)	Hospital outpatients with AD but without respiratory allergy (n = 201) versus outpatients with AD with respiratory allergy (n = 185) vs healthy control subjects (n = 510) versus control subjects without AD with respiratory allergy (n = 116)	Clinical evidence of AD (Rajka and Langeland criteria), χ^2 , sensitivity and specificity, odds ratio	Total serum IgE (>150 IU/mL) and specific IgE (Phadiatop) to common aeroallergens were not useful screening parameters because of their low sensitivity (32% to 49%), especially for those with AD but without concomitant respiratory allergy.
Diepgen et al, ³⁸ 1992 (Germany)	Hospital inpatients and outpatients with AD (n = 110) vs healthy rural and urban community control subjects (n = 527)	Clinical evidence of recurrent flexural dermatitis as the gold standard against Hanifin and Rajka major and minor criteria	Total serum IgE (>100 IU/mL) and specific IgE (Phadiatop) to common aeroallergens significantly associated with AD
Diepgen et al, ³⁹ 1996 (Germany)	Two studies: hospital patients with AD (n = 345) vs community control subjects (n = 618)—original study; hospital patients with AD (n = 106) vs healthy volunteers (n = 105) and control subjects with other skin diseases (n = 113)—validation study	Logistic regression and χ^2 analysis, clinical evidence of recurrent flexural dermatitis as the gold standard against Hanifin and Rajka criteria	Total IgE (>100 IU/mL) and increased specific IgE levels (Phadiatop) to common aeroallergens significantly associated with AD but no significant change in sensitivity or specificity of diagnostic criteria if IgE measurements excluded

TABLE VI. SPT responses and IgE antibodies and their predictive value in the development of AD

Reference	Study population	Study size	Diagnostic criteria*	Measurements	Quality score and results
Bergmann et al, ⁴¹ 1997 (Germany)	Birth cohort (selected) [†] vs newborn control subjects with no or low risk of allergic disease	499 vs 815	Clear	RAST, physical examination	3: no significant association between specific IgE and AD at 2 y
Zeiger et al, ⁴⁰ 1995 (United States)	Birth cohort (selected), [†] some on maternal-infant allergen avoidance diet	165	Clear	SPT, questionnaire diagnosis	2: all SPT responses at 12 mo have low positive predictive value for AD at age 7 y (32%)
Burr et al, ⁴² 1997 (United Kingdom)	Birth cohort (selected), [†] half of birth cohort on allergen avoidance diet	440	Not clear	SPT at 6 and 12 mo, RAST at 7 y, annual questionnaire re physician-diagnosed eczema and asthma between 2 and 7 y	1: SPT positivity to hen's egg at 12 mo significantly associated with AD at 7 y

*Diagnostic criteria: *not clear*, not clearly defined or validated; *clear*, clearly defined and validated (ie, derivatives of Hanifin and Rajka's criteria or physician diagnosis).

[†]Selected birth cohort is defined as being selection for positive family history of allergic disease.

the development of allergic respiratory disease by age 4 years.

Does knowledge of IgE sensitization increase our clinical predictive abilities in terms of predicting who might grow out of AD or who might best respond to certain treatments?

We found 2 studies that investigated whether IgE sensitization influenced disease prognosis in AD. In

particular, sensitization to hen's egg and cow's milk appeared associated with persistence of AD and disease severity in a recent study by Wolkerstorfer et al.³² Patients were 1 to 2 years old, had established AD, had a family history of allergic disease, and were followed up for 18 months. However, Novembre et al¹⁰ found no association between atopic state and AD persistence in a smaller hospital study. We did not identify any studies on the treatment responsiveness in patients with IgE-

TABLE VII. AD, SPT responses, and IgE antibodies and their predictive value in the development of allergic airway disease

Reference	Study population	Study size	Diagnostic criteria	Measurements (SPT, IgE antibodies, or both; atopic state)	Quality score (1-3) and outcome for any allergic disease
Nickel et al, ⁴⁷ 1997 (Germany)	Birth cohort	1314	Clear	IgE antibodies at 1, 2, and 3 y; follow-up at 1, 3, 6, 12, 18, 24, and 36 mo with structured interview and physical examination	3: AD no reliable predictor of aeroallergen sensitivity at age 3 y after multiple logistic regression
Bergmann et al, ⁴⁸ 1998 (Germany)	Birth cohort	1314	Clear	IgE antibodies at 1, 2, 3, and 5 y; physical examination and structured interviews at 1, 3, 6, 12, 18, and 24 mo	3: AD in the first 3 mo was a significant risk factor for aeroallergen sensitization at age 5 y (sensitivity, 12%; specificity, 97%; positive predictive value, 60%). For clinical asthma, sensitivity, specificity, and positive predictive value were 8%, 96%, and 28%, respectively.
Tariq et al, ⁴⁹ 2000 (United Kingdom)	Birth cohort	981	Clear	SPT at 1 and 2 y (only children with allergy) and 4 y (all children); physical examination at 1, 2, and 4 y	3: Significant association between clinical egg allergy during infancy and asthma and hay fever at age 4 y (odds ratio, 5.0; 95% CI, 1.1-22.3; positive predictive value, 55%; sensitivity and specificity not reported). Addition of AD to egg allergy increased positive predictive value to 80%, but the number was small (n = 10).
Lilja et al, ⁵⁰ 1996 (Sweden)	Birth cohort	134	Clear	IgE antibodies at 6 and 18 mo and 5 y; physical examination and questionnaire at 18 mo and 5 y	2: Any allergic disease at age 5 y (sensitivity, 40%; specificity, 95%; positive predictive value, 80%)
Laan et al, ⁵¹ 2000 (The Netherlands)	Birth cohort	133	Clear	IgE antibodies, SPT, physical examination at 6, 12, 18, and 24 mo	2: AD at 1 y not a risk factor for asthma in later life, but AD plus food sensitization associated with increased risk of asthma-like illness at 2 y.
Kulig et al, ⁵² 1998 (Germany)	Subgroup from Multiple Allergy Study (MAS); 49 children sensitized to inhalant allergens at 5 y vs 116 nonsensitized control subjects	49 vs 116	Clear	IgE antibodies; physical examination and structured interview at 1, 3, 6, 12, and 18 mo and 2, 3, 4, and 5 y	2: All participants with AD and IgE sensitization to at least one food allergen at age 12 mo had allergic airway disease by 5 y of age. Numbers were very small (n = 6).
Rhodes et al, ⁵³ 2001 (United Kingdom)	Birth cohort	100	Clear	SPT, physical examination where allergic disease suspected, follow-up every 3 mo for the first year and then annually until 5 y and at 11 y	2: AD before age 2 y not significantly associated with asthma in later life

associated AD versus those with non-IgE-associated AD.⁵⁴

DISCUSSION

The association between atopy and AD appears weaker and more complex than previously suggested. Up to two thirds of patients with AD have no measurable allergen-specific IgE antibody sensitization. The proportion of patients with AD who are atopic is greater in hospital studies, an observation that is partly the result of a difference in disease severity and also clearly related to study quality, with better studies showing a stronger atopy-AD association. Study quality might also explain part of the variation in the strength of association between atopy and AD observed between countries, especially where questionnaires were used to make a diagnosis of AD. Knowledge of IgE sensitization provided no predictive value when used as an additional factor as part of the diagnostic criteria. However, some evidence suggests that atopic individuals with AD are at an increased risk of allergic airway disease development and might have an overall poorer prognosis. Serum concentrations of IgE antibody to hen's egg at 12 months of age had the highest predictive value in this group.

We only included studies that defined atopy as either a positive SPT response or IgE antibodies by means of ImmunoCAP/RAST because total serum IgE levels, although associated with allergic disease, are highly influenced by other factors, such as smoking habits, outdoor pollution, and viral and parasitic infection.^{55,56} Apart from the definition of atopy, we attempted to be as comprehensive as possible in our literature search and resisted the temptation to use more restrictive inclusion criteria. This partly explains the considerable methodologic variation between surveys. For example, studies differ with regard to selection of participants, diagnostic criteria, disease severity spectrum, number and types of IgE sensitization measurements, age and ethnic group, severity measurement, follow-up times, laboratory and survey methodology, definition of atopic outcomes, and statistical analysis, making direct comparisons between studies in many cases very difficult. We used a predefined quality score to enhance comparability between studies and to demonstrate the effect of study quality on results. At the same time, we acknowledge that the scoring system used was derived empirically.

It is still unclear whether IgE sensitization is central to the development of AD, whether it is primarily an epiphenomenon of disease activity, or whether it is a cofactor for promoting certain gene-environment interactions. Well-conducted longitudinal studies using validated diagnostic criteria and clear definitions of atopy are needed to investigate whether there are differences in prognosis and treatment response between those prone and those not prone to IgE sensitization. These studies are complicated by the fact that the number of positive SPT responses and spectrum of IgE sensitization often changes

in the same individuals over time.¹⁰ In other words, not only the number of allergens tested for but also at what age measurements are performed will have a direct bearing on atopy prevalence. This will be particularly important for the determination of food-specific sensitization, which tends to occur already in infancy and, as opposed to sensitization to aeroallergens, is often transient.^{47,57}

Continued use of the term *atopic dermatitis* is problematic. Restricting the use of the terms *atopic dermatitis* or *atopic eczema* to atopic patients alone, as suggested by the EAACI/WAO, will help to reduce confusion and aid the continuing search for causative factors.

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